Glyxambi (Empagliflozin/Linagliptin): A Dual-Acting Oral Medication Approved for the Treatment of Patients with Type 2 Diabetes

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More than 29 million individuals in the United States have diabetes; of these, approximately 21 million people are diagnosed, and 8 million individuals remain undiagnosed and untreated.[1]

Type 2 diabetes, which accounts for the large majority of new diagnoses of diabetes, is a leading cause of morbidity, including cardiovascular disease, blindness, renal failure, amputations, and hospitalizations.[1,2] Type 2 diabetes is also associated with an increased risk for cancer, psychiatric illness, cognitive decline, chronic liver disease, arthritis, and other disabling conditions.[2]

Type 2 diabetes is a disorder in which the cells in the muscles, liver, and fat tissue are unable to use insulin effectively.[1] As the body's need for insulin increases, the beta cells in the pancreas lose their ability to produce sufficient quantities of the hormone. The relative role of insulin resistance compared with beta-cell dysfunction varies; some individuals are primarily insulin resistant, and others use insulin effectively but have low insulin secretion.[1] The risk for type 2 diabetes increases with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, and physical inactivity.[1]

The prevalence and the incidence of type 2 diabetes continue to escalate worldwide, resulting in a significant economic burden for healthcare systems.[2] The American Diabetes Association (ADA) estimates that the total (direct and indirect) cost of diabetes in the United States was $245 billion in 2012; the direct medical costs were $176 billion, and the indirect costs, including disability, work loss, and premature death, totaled approximately $69 billion.[3]

The treatment goals for patients with type 2 diabetes include the elimination of symptoms and the prevention of complications. Dietary and exercise modifications, as well as patient education, remain the cornerstones of initial treatment of patients with type 2 diabetes.[2] Antidiabetic medications are considered when these interventions are insufficient to maintain near-normal blood glucose levels and the patient's target hemoglobin (Hb) A_{1c} level.[2]

In recent years, glycemic management of patients with type 2 diabetes has become increasingly complex and even controversial.[2] New pharmacologic agents for type 2 diabetes have been introduced at a rapid rate, each with potential adverse effects. In addition, the benefits of intensive glucose control in preventing macrovascular complications remain uncertain. According to a joint position statement issued by the ADA and the European Association for the Study of Diabetes, metformin monotherapy represents the standard treatment for patients with diabetes at diagnosis, unless explicitly contraindicated.[2] If a patient's HbA_{1c} target level is not reached after approximately 3 months, one of several drugs can be combined with metformin.[2]

Drug classes and drugs that can be considered for adjunctive use with metformin include[2]:

- Sulfonylureas (glipizide, glimepiride, glyburide)
- Thiazolidinediones (pioglitazone)
- Dipeptidyl peptidase (DPP)-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin)
- Glucagon-like peptide (GLP)-1 receptor agonists (albiglutide, dulaglutide, exenatide, liraglutide)
- Insulins (glargine, lispro)
- Sodium-glucose transporter (SGLT)2 inhibitors (canagliflozin, empagliflozin).

Typically, the choice of treatment should be made on the basis of patient and medication characteristics, with the primary goal of improving glycemic control and minimizing the side effects.[2]

Glyxambi: A Novel Fixed-Dose Combination Agent for Type 2 Diabetes

On February 2, 2015, the US Food and Drug Administration (FDA) approved empagliflozin plus linagliptin (Glyxambi; Boehringer Ingelheim/Eli Lilly) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with empagliflozin and linagliptin is appropriate.[4] This fixed-dose combination contains 10 mg or 25 mg of empagliflozin and 5 mg of linagliptin, combining the properties of an SGLT2 and a DPP-4 in a single tablet.[5]

"Both of these classes of medications are safe and effective to lower the blood glucose, each through a different mechanism of action," said J. Michael Gonzalez-Campoy, MD, PhD, FACE, Medical Director and Chief Executive Officer of the Minnesota Center for Obesity,

Metabolism and Endocrinology. "Any time combination therapy is used, it is superior to monotherapy. Whenever two medications are combined into 1 pill, adherence improves, and usually the cost decreases."[6]

Empagliflozin and linagliptin are each FDA approved in single-ingredient oral formulations. Linagliptin was approved by the FDA in 2011 for the treatment of adults with type 2 diabetes, and empagliflozin was approved in August 2014.[7,8]

The empagliflozin plus linagliptin combination is not indicated for the treatment of patients with type 1 diabetes or those with diabetic ketoacidosis.[5] No studies of empagliflozin plus linagliptin combination have been conducted in patients with a history of pancreatitis; these patients may be at a high risk for pancreatitis while taking this fixed-dose combination.[5]

Mechanism of Action

Empagliflozin plus linagliptin therapy combines 2 medications with complementary mechanisms of action; empagliflozin is an SGLT2 inhibitor, and linagliptin is a DPP-4 inhibitor.[5] SGLT2 is a protein that facilitates the reabsorption of glucose from the kidney into the blood. By inhibiting SGLT2, empagliflozin lowers blood glucose

Table 1 Glycemic Parameters at 24 Weeks: Comparing Empagliflozin plus Linagliptin versus Each Drug Alone as Add-On Therapy in Patients Inadequately Controlled with Metformin

Efficacy parameter	Empagliflozin/ linagliptin 10 mg/5 mg	Empagliflozin/ linagliptin 25 mg/5 mg	Empagliflozin 10 mg	Empagliflozin 25 mg	Linagliptin 5 mg
HbA_{1c} level					
Patients, N	135	133	137	139	128
Baseline, mean, %	8.0	7.9	8.0	8.0	8.0
Change in HbA_{1c} from baseline, adjusted mean, %	–1.1	–1.2	–0.7	–0.6	–0.7
Comparison vs empagliflozin 25 mg or 10 mg, adjusted mean, %	–0.4 (95% CI, –0.6 to –0.2)	–0.6 (95% CI, –0.7 to –0.4)	—	—	—
Comparison vs linagliptin 5 mg, adjusted mean, %	–0.4 (95% CI, –0.6 to –0.2)	–0.6 (95% CI, –0.7 to –0.3)	—	—	—
Patients achieving HbA_{1c} <7%,[a] N (%)	74 (58)	76 (62)	35 (28)	43 (33)	43 (36)
Fasting plasma glucose					
Patients, N	133	131	136	137	125
Baseline, mean, mg/dL	157	155	162	160	156
Change from baseline, adjusted mean, mg/dL	–33	–36	–21	–21	–13
Comparison vs empagliflozin 25 mg or 10 mg, adjusted mean, mg/dL	–12 (95% CI, –18 to –5)	–15 (95% CI, –22 to –9)	—	—	—
Comparison vs linagliptin 5 mg, adjusted mean, mg/dL	–20 (95% CI, –27 to –13)	–23 (95% CI, –29 to –16)	—	—	—
Body weight					
Patients, N	135	134	137	140	128
Baseline, mean, kg	87	85	86	88	85
Percent change in weight from baseline	–3.1	–3.4	–3.0	–3.5	–0.7
Comparison vs empagliflozin 25 mg or 10 mg, adjusted mean, kg	0.0 (95% CI, –0.9 to 0.8)	0.1 (95% CI, –0.8 to 0.9)	—	—	—
Comparison vs linagliptin 5 mg, adjusted mean, kg	–2.4 (95% CI, –3.3 to –1.5)	–2.7 (95% CI, –3.6 to –1.8)	—	—	—

[a]Number of patients with HbA_{1c} levels >7% at baseline: empagliflozin 25 mg/linagliptin 5 mg, N = 123; empagliflozin 10 mg/linagliptin 5 mg, N = 128; empagliflozin 25 mg, N = 132; empagliflozin 10 mg, N = 125; linagliptin 5 mg, N = 119.
CI indicates confidence interval; HbA_{1c}, glycated hemoglobin.
Adapted from Glyxambi (empagliflozin and linagliptin) tablets prescribing information; January 2015.

levels and increases glucose excretion.[5] DPP-4 is an enzyme that cleaves GLP-1 and glucose-dependent insulinotropic polypeptide, 2 intestinal hormones that regulate the postprandial production of insulin and glucagon by the pancreas.[5]

As an inhibitor of DPP-4, linagliptin increases the concentrations of these incretin hormones, which stimulates the release of insulin in a glucose-dependent manner and decreases glucagon levels in the blood. GLP-1 also reduces glucagon secretion from the pancreas, which results in lowered glucose production by the liver.[5]

Dosing and Administration

Empagliflozin plus linagliptin fixed-dose combination should be started at 10 mg empagliflozin/5 mg linagliptin, taken once daily in the morning, with or without food. The higher dose of empagliflozin plus linagliptin (25 mg empagliflozin/5 mg linagliptin) once daily may be considered if the initial dose is well-tolerated.[5]

No data are available regarding the safety and efficacy of empagliflozin plus linagliptin in patients who previously received other oral antihyperglycemic agents and switched to empagliflozin plus linagliptin.[5]

Clinical Trials

The approval of empagliflozin plus linagliptin was based on a double-blind, phase 3 clinical trial that compared the safety and efficacy of empagliflozin plus linagliptin with the individual drugs, empagliflozin (10 mg or 25 mg) and linagliptin (5 mg), in adults with inadequately controlled type 2 diabetes despite taking at least 1500 mg of metformin.[4,5,9]

After a single-blind, placebo run-in period of 2 weeks, 686 patients with type 2 diabetes whose disease remained inadequately controlled (HbA_{1c} levels, 7.0%-10.5%) were randomized to 1 of 5 active-treatment arms.[5,9] The study's primary end point was the change from baseline in HbA_{1c} levels at week 24. The secondary end points included the change from baseline in fasting plasma glucose levels at week 24, the change from baseline in body weight at week 24, and the proportion of patients with baseline HbA_{1c} levels ≥7% who reached HbA_{1c} levels <7% at week 24.[9]

After 24 weeks of treatment, the combination of empagliflozin plus linagliptin demonstrated a significant improvement in the HbA_{1c} levels (P <.001) and fasting plasma glucose levels (P <.001) compared with empagliflozin monotherapy and linagliptin monotherapy (**Table 1**).[5,9]

Although not approved for lowering weight, daily treatment with both formulations of empagliflozin plus linagliptin also resulted in a significant reduction in body weight compared with linagliptin alone (P <.001)[4,5,9]; no significant differences in body weight were observed when empagliflozin plus linagliptin was compared with empagliflozin alone (Table 1).[5,9]

Table 2 Adverse Reactions in ≥2% of Patients Receiving Empagliflozin and More Often Than in Patients Receiving Placebo

Adverse reaction	Empagliflozin 10 mg, %	Empagliflozin 25 mg, %	Placebo, %
Urinary tract infection	9.3	7.6	7.6
Female genital mycotic infections	5.4	6.4	1.5
Upper respiratory tract infections	3.1	4.0	3.8
Increased urination	3.4	3.2	1.0
Dyslipidemia	3.9	2.9	3.4
Arthralgia	2.4	2.3	2.2
Male genital mycotic infections	3.1	1.6	0.4
Nausea	2.3	1.1	1.4

Adapted from Glyxambi (empagliflozin and linagliptin) tablets prescribing information; January 2015.

Table 3 Adverse Reactions in ≥2% of Patients Receiving Linagliptin and More Often Than in Patients Receiving Placebo

Adverse reaction	Linagliptin 5 mg, %	Placebo, %
Nasopharyngitis	7.0	6.1
Diarrhea	3.3	3.0
Cough	2.1	1.4

Adapted from Glyxambi (empagliflozin and linagliptin) tablets prescribing information; January 2015.

Safety

The safety of empagliflozin plus linagliptin (empagliflozin 10 or 25 mg/linagliptin 5 mg) was evaluated in 1363 patients with type 2 diabetes who received treatment for a maximum of 52 weeks in active-controlled clinical trials.[5] Based on pooled analyses of these studies, the most common adverse reactions associated with empagliflozin plus linagliptin therapy included urinary tract infection (a predefined adverse event grouping that also includes asymptomatic bacteriuria and cystitis), nasopharyngitis, and upper respiratory tract infection.[5]

Table 2 summarizes the adverse events that occurred in ≥2% of patients who received empagliflozin and that occurred more frequently than in patients who received placebo.[5] Because empagliflozin causes osmotic diuresis,

intravascular volume contraction and side effects related to volume depletion can occur.[5]

Table 3 lists the adverse events that occurred in ≥2% of patients who received linagliptin and that occurred more frequently than in patients who received placebo.[5] Hypersensitivity and myalgia were also reported in clinical studies of linagliptin monotherapy.[5]

Hypoglycemia was reported among patients taking empagliflozin plus linagliptin during a period of 52 weeks (**Table 4**).[5]

Warnings and Precautions

Pancreatitis. Acute pancreatitis, including fatal pancreatitis, has been reported in patients taking linagliptin.[5] If pancreatitis is suspected, empagliflozin plus linagliptin should be discontinued and appropriate management should be initiated. This combination has not been studied in patients with a history of pancreatitis.[5]

Hypotension. Because empagliflozin causes intravascular volume contraction, symptomatic hypotension can occur, particularly in patients with renal impairment, with low systolic blood pressure, in elderly patients, and in patients taking diuretic agents. Before starting empagliflozin plus linagliptin therapy, the volume status should be assessed and corrected as needed. Patients should be monitored for the signs and symptoms of hypotension, particularly in clinical situations in which volume contraction is expected.[5]

Impairment in renal function. Empagliflozin is known to increase serum creatinine levels and to decrease estimated glomerular filtration rate (eGFR).[5] Elderly patients and patients with moderate renal impairment are at an increased risk for renal function impairment while taking empagliflozin. Renal function should be evaluated before starting empagliflozin plus linagliptin and frequently thereafter.[5]

Hypoglycemia with concomitant use with insulin and insulin secretagogues. In a placebo-controlled clinical trial, the rates of hypoglycemia were higher when empagliflozin or linagliptin was used in combination with an insulin secretagogue (eg, sulfonylurea) or with insulin. When used in combination with empagliflozin plus linagliptin therapy, a lower dose of the insulin secretagogue or insulin may be required.[5]

Table 4 Incidence of Overall and Severe Hypoglycemic Adverse Reactions with Empagliflozin plus Linagliptin

Add-on to metformin after 52 weeks	Empagliflozin 10 mg/ linagliptin 5 mg, % (N = 136)	Empagliflozin 25 mg/ linagliptin 5 mg, % (N = 137)
Hypoglycemic events, overall[a]	2.2	3.6
Hypoglycemic events, severe[b]	0	0

[a]Plasma or capillary glucose of ≤70 mg/dL or requiring assistance.
[b]Requiring assistance regardless of blood glucose.
Adapted from Glyxambi (empagliflozin and linagliptin) tablets prescribing information; January 2015.

Genital mycotic infections. Genital mycotic infections have been reported by patients who received empagliflozin. Patients with a history of chronic or recurrent genital mycotic infections are more likely to develop these infections while taking empagliflozin plus linagliptin compared with patients without these characteristics; these patients should be monitored appropriately.[5]

Urinary tract infections. Patients receiving empagliflozin are at a higher risk for urinary tract infections, and should be monitored appropriately.[5]

Hypersensitivity reactions. During postmarketing surveillance, serious hypersensitivity reactions (eg, anaphylaxis, angioedema, exfoliative skin conditions) were reported in patients who received linagliptin. These reactions typically occurred within the first 3 months after starting linagliptin treatment, with some reactions occurring after the first linagliptin dose.[5]

If a serious hypersensitivity reaction is suspected, empagliflozin plus linagliptin therapy should be discontinued and alternative treatment for diabetes should be started.[5] Because angioedema has been reported with other DPP-4 inhibitors, caution should be taken when considering empagliflozin plus linagliptin for patients who have experienced angioedema after taking another DPP-4 inhibitor.[5]

Increased low-density lipoprotein cholesterol (LDL-C) levels. Increases in LDL-C levels can occur with empagliflozin. Lipid levels should be monitored and treated as needed.[5]

Macrovascular outcomes. No clinical studies have demonstrated conclusive evidence of the reduction in macrovascular risk with empagliflozin plus linagliptin therapy or with any other antidiabetic drug.[5]

Use in Specific Populations

Pregnancy. Empagliflozin plus linagliptin combination has been assigned pregnancy category C; there are no adequate and well-controlled studies with this drug in pregnant women. This combination should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus.[5]

Nursing mothers. It is not known whether the components of empagliflozin plus linagliptin are present in human breast milk. Either nursing or empagliflozin plus linagliptin therapy should be discontinued on the basis of the importance of the drug to the mother.[5]

Pediatric use. The safety and efficacy of empagliflozin

plus linagliptin have not been established in pediatric patients aged <18 years.[5]

Geriatric use. Empagliflozin is associated with osmotic diuresis, which could affect hydration in patients aged ≥75 years.[5] The efficacy of empagliflozin is diminished in elderly patients with renal impairment. In addition, the risk for urinary tract infections increased among patients aged ≥75 years who received empagliflozin. No dosage adjustment of empagliflozin or linagliptin is recommended in elderly patients.[5]

For patients whose type 2 diabetes is inadequately controlled with high-dose metformin, this novel combination drug, with a combined mechanism of action, may enhance drug adherence and glycemic control.

Renal impairment. Empagliflozin plus linagliptin is contraindicated in patients with severe renal impairment (eg, eGFR <30 mL/min/1.73 m^2) or with end-stage renal disease, and in patients undergoing dialysis.[5] The risks for renal impairment, volume depletion, and urinary tract infections are higher among patients with renal dysfunction compared with patients without renal dysfunction.[5]

Hepatic impairment. No dosage adjustment of empagliflozin plus linagliptin is necessary for patients with mild, moderate, or severe hepatic impairment.[5]

Conclusion

Control of glucose and HbA_{1c} levels is key to preventing complications of diabetes. Some experts have suggested that reaching and maintaining glucose control early in patients with type 2 diabetes may result in benefits that persist beyond the treatment period.[10] Empagliflozin plus linagliptin, a dual-acting oral tablet, has demonstrated superior efficacy and acceptable safety in a large phase 3 clinical trial of patients with poorly controlled type 2 diabetes compared with patients who received empagliflozin or linagliptin monotherapy. For patients whose type 2 diabetes is inadequately controlled with high-dose metformin, this novel combination drug, with a combined mechanism of action, may enhance drug adherence and glycemic control. ■

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